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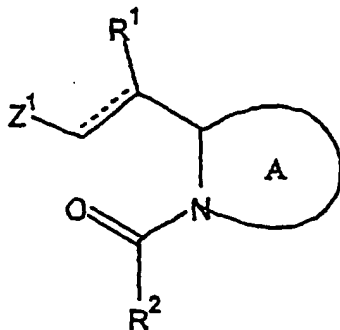
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ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.

(54) Title: N-ACYLPYRROLIDIN-2-YLALKYLBENZAMIDINE DERIVATIVES AS INHIBITORS OF FACTOR XA

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(I)

(57) Abstract: This invention is directed to a compound of formula (I) which is useful for inhibiting the activity of Factor Xa, by contacting said compound with a composition containing Factor Xa. The present invention is also directed to compositions containing compounds of formula (I), methods for their preparation, their use, such as in inhibiting the formation of thrombin or for treating a patient suffering from, or subject to, a disease state associated with a physiologically detrimental excess amount of thrombin.

# INTERNATIONAL SEARCH REPORT

International Application No

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## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D207/08 C07D401/10 C07D471/04 C07D403/06 C07D409/06  
A61K31/40 A61K31/4025 A61P7/02

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, EPO-Internal, WPI Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages   | Relevant to claim No.        |
|------------|--|------------------------------|
| X          | WO 98 01428 A (DU PONT MERCK PHARMA)<br>15 January 1998 (1998-01-15)<br>page 1, line 6 - line 11; claim 1; table 5<br>---  | 1-29                         |
| X          | WO 97 45424 A (HONG WOO SANG ;KIM JONG MIN<br>(KR); KOO BON AM (KR); MIN JAE KI (KR))<br>4 December 1997 (1997-12-04)<br>claims 1,5; table 1<br>---  | 1-23,25,<br>27               |
| X          | HAN W T ET AL: "AZETIDIN-2-ONE<br>DERIVATIVES AS INHIBITORS OF THROMBIN"<br>BIOORGANIC & MEDICINAL CHEMISTRY, ELSEVIER<br>SCIENCE LTD, GB,<br>vol. 3, no. 8, 1995, pages 1123-1143,<br>XP000612953<br>ISSN: 0968-0896<br>page 1131, line 6 - line 20; table 1<br>---<br>-/-- | 1,5,6,<br>15,16,<br>19,25,27 |



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

### \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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\*G\* document member of the same patent family

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## INTERNATIONAL SEARCH REPORT

International Application No

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages   | Relevant to claim No.       |
|------------|--|-----------------------------|
| X          | WO 98 33797 A (WATANABE FUMIHIKO ; SHIONOGI & CO (JP); OHTANI MITSUAKI (JP); SENO)<br>6 August 1998 (1998-08-06)<br>page 100<br>---  | 1,5,6,<br>9-12,15,<br>16,19 |
| X          | DATABASE CHEMABS 'Online!<br>CHEMICAL ABSTRACTS SERVICE, COLUMBUS,<br>OHIO, US;<br>ARISAWA, MITSUHIRO ET AL: "Synthesis of<br>chiral bicyclic lactams using ring-closure<br>metathesis. Synthesis of (-)-coniceine and<br>(S)-pyrrolam A"<br>retrieved from STN<br>Database accession no. 127:358978<br>XP002163919<br>Pyrrolidine,1-(1-oxo-4-pentenyl)-2-(2-phen<br>ylethenyl)-, 'S-(E)!- (RN 198218-79-0)<br>& SYNLETT (1997), (10), 1179-1180 ,<br>---  | 1,5,6,9,<br>10,15,16        |
| X          | DATABASE CHEMABS 'Online!<br>CHEMICAL ABSTRACTS SERVICE, COLUMBUS,<br>OHIO, US;<br>OKADA, MIDORI ET AL: "Fluoro-lactonization<br>of 4-alkenoic acid derivatives with<br>N-fluoropentachloropyridinium triflate"<br>retrieved from STN<br>Database accession no. 127:81322<br>XP002163920<br>2-Pyrrolidinone,1-acetyl-5-(fluoromethyl)-<br>5-(2-phenylethyl)- (RN 191856-33-4)<br>& J. FLUORINE CHEM. (1997), 82(2), 157-161<br>,<br>---  | 1,5,6,9,<br>10,15,<br>16,19 |
| X          | DATABASE CHEMABS 'Online!<br>CHEMICAL ABSTRACTS SERVICE, COLUMBUS,<br>OHIO, US;<br>NEUKOMM, G. ET AL: "Organic natural<br>products. Part 188. Structure of<br>hypercratine, another alkaloid of Ruspolia<br>hypercrateriformis"<br>retrieved from STN<br>Database accession no. 100:64931<br>XP002163921<br>Pyrrolidine,1-acetyl-2-'7-'2-(1-acetyl-2-p<br>yrrolidinyl)ethyl!-2,3-dihydro-3-(4-hydrox<br>y-3-methoxyphenyl)-1,4-benzodioxin-2-yl!-<br>(RN 88607-26-5) &<br>Pyrrolidine,1-acetyl-2-'7-'2-(1-acetyl-2-p<br>yrrolidinyl)ethyl!-3-(3,4-dimethoxyphenyl)<br>-2,3-dihydro-1,4-benzodioxin-2-yl!-<br>(RN 88607-27-6)<br>& PLANTA MED. (1983), 48(4), 246-52 ,<br>--- | 1,5,6,9,<br>10,15,<br>16,19 |
|            | ---  | -/--                        |

## INTERNATIONAL SEARCH REPORT

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages  | Relevant to claim No.                 |
|------------|---|---------------------------------------|
| X          | <p>DATABASE CHEMABS 'Online!<br/> CHEMICAL ABSTRACTS SERVICE, COLUMBUS,<br/> OHIO, US;<br/> HERBERT, RICHARD B. ET AL: "Synthesis of<br/> (.+-.)-norruspoline"<br/> retrieved from STN<br/> Database accession no. 98:89708<br/> XP002163922<br/> Pyrrolidine,1-acetyl-2-'2-'3-methoxy-4-(ph<br/> enylmethoxy)phenyl!ethenyl!- (RN<br/> 84638-20-0) &amp;<br/> Pyrrolidine,1-acetyl-2-'2-'3-(acetyloxy)-4<br/> -methoxyphenyl!ethenyl!- (RN 84638-22-2)<br/> &amp; J. CHEM. RES., SYNOP. (1982), (11), 299</p>  | 1,5,6,9,<br>10,15,16                  |
| X          | <p>---<br/> DATABASE CHEMABS 'Online!<br/> CHEMICAL ABSTRACTS SERVICE, COLUMBUS,<br/> OHIO, US;<br/> ROESSLER, FELIX ET AL: "Ruspolia<br/> hypercrateriformis M.R.: Isolation and<br/> structure elucidation of new pyrrolidine<br/> alkaloids"<br/> retrieved from STN<br/> Database accession no. 89:43871<br/> XP002163923<br/> Pyrrolidine,1-acetyl-2-'2-'4-(acetyloxy)-3<br/> -methoxyphenyl!ethenyl!-, (RN 67257-63-0)<br/> &amp;<br/> Pyrrolidine,1-acetyl-2-'2-'4-(acetyloxy)-3<br/> -methoxyphenyl!ethyl!- (RN 67257-65-2)<br/> &amp; HELV. CHIM. ACTA (1978), 61(3), 1200-6 ,</p> | 1,5,6,9,<br>10,15,<br>16,19           |
| P, X       | <p>---<br/> WO 00 37458 A (SCHERING CORP)<br/> 29 June 2000 (2000-06-29)<br/><br/> pages 145, 172-177, 180, 181, 231, 242,<br/> 243, 246, 247<br/> claim 1<br/><br/> ---<br/> -/--</p>  | 1,5,6,<br>9-11,13,<br>15,16,<br>19,22 |

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 00/10890

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages  | Relevant to claim No.             |
|------------|---|-----------------------------------|
| P, X       | <p>DATABASE CHEMABS 'Online!<br/>CHEMICAL ABSTRACTS SERVICE, COLUMBUS,<br/>OHIO, US;<br/>ARISAWA, MITSUHIRO ET AL: "Construction of<br/>chiral 1,2-cycloalkanopyrrolidines from<br/>L-proline using ring closing metathesis<br/>(RCM)"<br/>retrieved from STN<br/>Database accession no. 134:42302<br/>XP002163924<br/>Pyrrolidine, 1-(1-oxo-3-butenyl)-2-('(1E)-2-<br/>phenylethenyl)-, (2S)- (RN 311797-64-5)<br/>&amp; CHEM. PHARM. BULL. (2000), 48(10),<br/>1593-1596 ,</p> <p>-----</p> | <p>1,5,6,<br/>9-12,15,<br/>16</p> |

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP 00/10890

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 26 - 29 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 1-29 (all partially)  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-29 (all partially)

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT).

Moreover, the present claims do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The functional terms "prodrug" and "acid bioisostere" do not enable the skilled person to determine which technical features are necessary to perform the stated function. It is thus unclear which specific compounds fall within the scope of said claim. A lack of clarity within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible.

For these reasons, a meaningful search over the whole breadth of the claims is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely, compounds of formula I where ring A is a pyrrolidiny ring, i.e. compounds according to claim 10, excluding prodrugs and acid bioisosteres.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 00/10890

| Patent document<br>cited in search report | Publication<br>date | Patent family<br>member(s)  | Publication<br>date  |
|---|---------------------|---|--|
| WO 9801428 A                              | 15-01-1998          | AU 3645697 A<br>CA 2259573 A<br>EP 0960102 A  | 02-02-1998<br>15-01-1998<br>01-12-1999   |
| WO 9745424 A                              | 04-12-1997          | AU 3049497 A<br>CN 1219932 A<br>EP 0918768 A<br>JP 2000504030 T   | 05-01-1998<br>16-06-1999<br>02-06-1999<br>04-04-2000   |
| WO 9833797 A                              | 06-08-1998          | AU 719210 B<br>AU 5577598 A<br>BR 9807132 A<br>CN 1251587 T<br>EP 0976748 A<br>NO 993706 A<br>PL 334915 A<br>US 6147100 A | 04-05-2000<br>25-08-1998<br>25-01-2000<br>26-04-2000<br>02-02-2000<br>30-09-1999<br>27-03-2000<br>14-11-2000 |
| WO 0037458 A                              | 29-06-2000          | AU 2347900 A  | 12-07-2000   |